REMARKS

Upon entry of the present amendments, claims 1-6, 13-25, 27-38, and 40-45 will be pending in this application. Claims 1-6 and 13-23 remain withdrawn. Applicants have amended claims 24, 25, 27-30, 32-35, 40, and 45, and canceled claims 26 and 39 without prejudice or disclaimer. Support for the amendments to claims 24 and 35 can be found in the application, e.g., at page 29, lines 4-23 of the specification and in canceled claims 26 and 39. Support for the amendment to claim 25 can be found, e.g., at page 29, lines 4-23 of the specification. The amendments to claims 27-30, 32-34, 40, and 45 merely change the claim dependencies. No new matter has been added.

Examiner Interview

Applicants thank Examiner Gussow and Supervisory Patent Examiner Larry Helms for conducting a telephonic interview with Applicants' representatives on November 19, 2007.

During the interview, the rejections of the examined claims under 35 U.S.C. §§ 102 and 103 and the above amendments to claims 24 and 35 were discussed. Examiners Gussow and Helms indicated that these amendments would likely overcome the rejections of record.

35 U.S.C. § 102

The Office alleges that claims 24, 28-35, and 41-45 are anticipated by DeNardo et al. (*Cancer Biotherapy & Radiopharmaceuticals* 16:525-535 (2001); "DeNardo").

Solely in the interest of expediting prosecution, Applicants have amended claim 24 to recite a method for producing an HLA class I antigen-recognizing minibody, and claim 35 to recite a method of producing a minibody, the CDRs of which are derived from the CDRs of an HLA class I antigen-recognizing whole antibody. The amendments to claims 24 and 35 introduce elements from claims 26 and 39 (respectively), which claims were not rejected in light of DeNardo, and in fact these elements are not disclosed in De Nardo. Applicants submit that

these amendments overcome this rejection of claims 24 and 35 (and their dependencies 28-34 and 41-45), and respectfully request that this rejection of these claims be withdrawn.

35 U.S.C. § 103

The Office alleges that claims 24-45 are obvious in light of Oka et al. (*Sankyo Seimei Kagaku Kenkyu Shinko Zaidan Kenkyu Hokokushu* 12:46-56 (1998); "Oka"), Kimura et al. (*Biochemical and Biophysical Research Communications* 325:1201-1209 (2004); "Kimura"), and Ledbetter et al. (*Critical Reviews in Immunology* 17:427-435 (1997); "Ledbetter"). Claims 26 and 39 have been canceled. Applicants traverse the rejection as applied to the remaining claims.

According to the Office action at pages 7-8,

> Oka, et al. teach a whole antibody 2D7 that binds to HLA an HLA-A class I antigen. Oka, et al., do not teach a minibody of the 2D7 antibody. This deficiency is made up for in the teachings of Ledbetter, et al.
>
> Ledbetter, et al. teach that a single chain Fv (scFv or sFv) G28-5sFv is a more potent agonist for CD40 responses than the parental full length G28-5 IgG.
>
> It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced an HLA-recognizing minibody using the full length parent [antibody 2D7] of Oka, et al. and result in a minibody with increased cytotoxic activity in view of Ledbetter, et al.
>
> One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a minibody with increased cytotoxic activity of Ledbetter, et al. with the parent antibody of Oka, et al. because Ledbetter, et al. teach that the scFv antibody had increased activity relative to the parent full-length antibody and Kimura, et al. teach that the 2D7 antibody of Oka, et al. is an agonist antibody.

The Office seems to believe that Ledbetter's and Oka's teachings, combined with those of Kimura, provide both a motivation to make a minibody of Oka's 2D7 antibody, and an expectation of success upon doing so. This rationale fails on a number of grounds.

First, Kimura is not even prior art. The present application is a U.S. national phase filing (under 35 U.S.C. § 371) of international application no. PCT/JP03/13063. Under to 35 U.S.C. § 365, the present application is entitled to the benefit of the October 10, 2003, filing date of the

international application. This filing date precedes the November 11, 2004, publication date of Kimura. As a result, Kimura is not a proper reference for the Office to rely upon in making its obviousness rejection.

Applicants note that, under certain circumstances, a post-filing date reference such as Kimura may be relied upon to show that a claimed composition inherently possessed some property that is specified as a limitation of the claim, e.g., to support a rejection for inherent anticipation. That is not the situation here. In the present case, the post-filing date reference is relied upon to fill a gap in the logic of the asserted motivation to combine Oka with Ledbetter. The Office theorizes that it would have been obvious to make an scFv form of Oka's 2D7 antibody because, according to the Office action, Ledbetter et al. taught that an scFv of a different antibody, G28-5 Ig, possessed an agonist activity that was greater than that of the full-length G28-5 Ig, and Kimura taught that 2D7 possessed agonist activity. Thus, the teachings of the Kimura reference are relied upon to support the Office's theory that those of skill in the art would have had a motivation to make an scFv form of 2D7. Because Kimura was published after the priority date of the present application, it was not available to those in the art at the priority date and cannot be relied upon to show those of ordinary skill in the art had either the necessary motivation to select 2D7 as an agonist, or the necessary expectation of success. (Clearly, if a person did not know the information in Kimura, he/she could not base a motivation or expectation on it.) Accordingly, Applicants submit that the Office has failed to establish a prima facie case of obviousness on this basis alone.

Second, there is no logical reason to jump from Ledbetter's teachings about G28-5 IgG and its scFv to a conclusion that Oka's 2D7 antibody should be prepared as an scFv. The art taught no significant similarities between the G28-5 IgG antibody and 2D7 that might have inspired one of ordinary skill to combine Ledbetter's and Oka's teachings. Quite the opposite:

- Ledbetter describes the G28-5 IgG antibody as binding to the CD40 receptor, a member of the TNF family of receptors (page 427, left column), while Oka did not characterize the antigen to which 2D7 binds other than to identify it as a 45kD cell surface protein on RPMI 8266 cells. (The 45kD cell surface protein of Oka is now known to be HLA-A class I antigen, but that was a

discovery by the present inventors and was not disclosed in Oka. HLA-A class I is entirely unrelated to the TNF receptor family.)

- Ledbetter says that the full length G28-5 IgG antibody possesses both agonist and antagonist activities (page 427, text bridging left and right columns). In contrast, Oka did not even hazard a guess as to whether the 2D7 antibody was acting as an agonist, antagonist, both, or neither.

- According to Ledbetter, G28-5 scFv's agonist activity results in an increase in cellular proliferation (page 428, right column). In contrast, Oka teaches that the 2D7 antibody's activity is essentially the opposite: an inhibition of protein synthesis.

Given the striking differences between Ledbetter's antibody and that disclosed by Oka, there was simply no logical reason to apply Ledbetter's teachings about G28-5 scFv to the antibody of Oka.

Third, the full length G28-5 antibody in Ledbetter exhibits both agonist and antagonist effects on CD40. Ledbetter had predicted, based on results with a G28-5 Fab fragment, that the G28-5 scFv studied therein would act as an antagonist of CD40 (see, e.g., page 427, right column). Ledbetter expressed surprise that in fact, the scFv turned out to behave in the opposite manner, as a CD40 agonist, and indeed, it was a more potent agonist than the full length antibody (see, e.g., page 428, right column, section C, last paragraph). The Abstract states "Surprisingly, G28-5 sFv was a potent CD40 agonist that rapidly crosslinked CD40 on the cell surface…", and further states "G28-5 sFv was a more potent agonist than G28-5 IgG …" Further, the G28-5 sFv acquired new properties "[t]hese results indicate that G28-5 sFv is a full agonist on B cells …" (page 429, left column; emphasis added), in contrast to the parent IgG. There is no reason to expect, based on the cited art, that these surprising results observed by Ledbetter would also occur with an scFv of a completely unrelated antibody that acts on a completely different type of cell surface molecule with an completely unrelated signaling pathway to produce a completely different outcome (cytotoxicity vs. cellular proliferation).

The scFv in Ledbetter possessed properties that were unexpected and unpredictable from the properties of the full length antibody, and even acquired a novel property not possessed by the parent molecule. From these results, a skilled practitioner would not have had any reasonable expectation that a minibody (e.g., scFv) of a whole antibody that recognizes an HLA class I antigen would retain a specific property (cytotoxic activity) of the whole antibody, much less have an expectation that the scFv would have an increased activity as compared to the whole antibody.

Finally, Oka and Ledbetter offer no teaching or suggestion to test a minibody for cytotoxic activity. Claim 24 has been amended to recite the step of assaying a cytotoxic activity of the minibody. Claim 35 recites a similar step: confirming that the expressed minibody possesses cytotoxic activity greater than that of the whole antibody. Oka makes no teaching or suggestion whatsoever regarding minibodies and thus also fails to teach or suggest testing minibodies for cytotoxic activity. As discussed above, the G28-5 scFv in Ledbetter caused increased cellular proliferation. This reference is devoid of any possible reason to assay an scFv (or any minibody) for cytotoxic activity, or to determine if the minibody has greater cytotoxic activity than the whole antibody.

Applicants submit that the Office has not established a *prima facie* case of obviousness against claims 24, 25, 27-38, and 40-45 (claims 26 and 39 have been canceled) based the combination of Oka, Ledbetter, and Kimura. Withdrawal of the obviousness rejection of claims 24, 25, 27-38, and 40-45 is requested.

CONCLUSION

Applicants respectfully submit that all of the pending claims are in condition for allowance, which action is requested. Applicants do not concede any positions of the Examiner that are not expressly addressed above, nor do Applicants concede that there are not other good reasons for patentability of the presented claims or other claims.

No fees are believed to be due. Please apply any charges or credits to deposit account 06-1050, referencing Attorney Docket No. 14875-141US1.

Respectfully submitted,

Date: Dec. 6, 2007

Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819
Reg. No. 59,651

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

21774554.doc